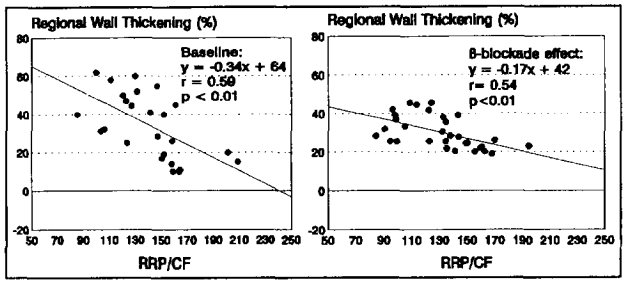
chemia lasting 1.25 (n = 18), 2.5 (n = 20), 5 (n = 9), or 10 (n = 16) min, or multiple episodes cumulating in 10 (2 × 5 min, n = 17) or 20 (4 × 5 min, n = 13 or 2 × 10 min, n = 14) min of preconditioning ischemia time, all followed by 5 min of reperfusion. Control rats (n = 22) were not preconditioned. In separate groups, glycogen was determined before whereas infarct size was determined after prolonged ischemia (45 min) and reperfusion (120 min). Myocardial glycogen levels and infarct size are shown as a function of preconditioning ischemia time.



In addition, infarct size reduction correlated with glycogen depletion before prolonged ischemia ($r = 0.98$; 19 $p < 0.001$). Thus, increasing preconditioning ischemia time results in progressive myocardial glycogen depletion and infarct size reduction, reaching a maximal effect when the preconditioning ischemia time is ≥5 min. This maximal effect may be due to marked depletion of myocardial glycogen stores before prolonged ischemia.

10:45

706-2 Adenosine-mediated Myocardial Protection During Preconditioning is Abolished by K_{ATP} Channel Blockade in Rabbits

John G. Kingma Jr., Mette Hazenberg, Denis Simard, Jacques R. Rouleau. *Laval University, Quebec, Canada*

The anti-infarct effect of ischemic preconditioning (PC) is partly due to adenosine receptor-mediated opening of K_{ATP} channels. PC-mediated protection may be potentiated by exogenous infusion of adenosine receptor agonists. To test this hypothesis, pentobarbital anesthetized rabbits (n = 8/group) underwent two cycles of 5 min regional ischemia and 5 min coronary reperfusion (REP; i.e., PC) followed by 30 min ischemia and 3 h REP. Rabbits received either adenosine (AD; 0.01 mg/min); cyclopentyladenosine (CP; A_1 receptor agonist; 0.001 mg/min) or CGS 21680 (CG; A_2 receptor agonist; 0.01 mg/min), *i.v.* for 65 min starting 5 min before onset of REP. K_{ATP} channels were blocked with *i.v.* glibenclamide (G; 0.15 mg/kg) 10 min before PC in the absence or presence of AD, CP or CG. Infarct and risk (R; cm^3) volume was assessed with tetrazolium and microsphere autoradiography. Infarct size (IS) was normalized to R. IS in absolute controls (i.e., no PC) was 51 ± 6% (mean ± SEM).

	PC	G + PC	AD	G + AD	CP	G + CP	CG	G + CG
R	1.6 ± 1	1.8 ± 0.2	1.6 ± 0.2	1.4 ± 0.1	1.9 ± 0.1	1.4 ± 0.3	2.0 ± 0.2	1.2 ± 0.1
IS	19 ± 2	39 ± 7†	27 ± 7	37 ± 6†	12 ± 1	44 ± 9†	22 ± 3	50 ± 5†

†$p \leq 0.05$; one-way ANOVA and SNK multiple range test

Cardiodynamics were similar for the treatment groups; but heart rate-blood pressure product was lower ($p \leq 0.05$) during CP infusion. *Conclusions:* 1) PC markedly reduced IS; 2) PC-mediated protection was not potentiated with exogenous AD, CP or CG; and 3) G abolished PC-mediated protection without/with exogenous AD, CP or CG. These data indicate that adenosine receptor activation and opening of K_{ATP} channels are involved in PC.

11:00

706-3 The Protein Kinase C Inhibitor Polymyxin-B does not Block Preconditioning-induced Cardioprotection in the Canine Model

Karin Przyklenk, Robert A. Kloner. *Heart Institute, Hospital of the Good Samaritan, Los Angeles, CA; University of Southern California, Los Angeles, CA*

In the rabbit model, administration of protein kinase C (PKC) inhibitors such as polymyxin-B have been reported to attenuate the reduction in infarct size achieved with ischemic preconditioning. Activation of PKC has therefore been proposed to play a crucial role in the mechanism by which preconditioning protects the heart from subsequent sustained coronary occlusion (CO). However, the possible confounding effects of PKC inhibition on myocardial blood flow were not assessed in these studies. We addressed this issue in 28 dogs subjected to 1 h of sustained CO and 4–5 h of reperfusion. In Protocol I, dogs received 45-min episodes of preconditioning ischemia (PC: n = 7) or a comparable control period (n = 9) before sustained CO; Protocol II was identical except polymyxin-B (PMX: 50 mg/kg) was administered throughout the PC regimen (n = 6) or control period (n = 6). Blood flow to the ischemic subendocardium was assessed during sustained CO by injection of radiolabeled microspheres, and area of necrosis (AN) was delineated by tetrazolium staining and expressed as a % of the area at risk of infarction (AR).

		Endo Flow (ml/min/g)	AN/AR (%)
Protocol I:	*Control*	0.06 ± 0.02	19 ± 3
	PC	0.09 ± 0.03	6 ± 2**
Protocol II:	*Control + PMX*	0.01 ± 0.01	29 ± 5
	PC + PMX	0.02 ± 0.01	10 ± 3§

** $p < 0.01$ vs Control; § $p < 0.01$ vs Control + PMX

Protocol I confirmed the expected reduction in infarct size in preconditioned dogs vs. controls. Protocol II revealed that all PMX-treated dogs were rendered profoundly ischemic during CO. Nonetheless, treatment with PMX did not attenuate the reduction in infarct size achieved with preconditioning. Thus, the PKC inhibitor polymyxin-B may exacerbate ischemia during CO: this may contribute to the previously reported "increase" in infarct size in preconditioned rabbits treated with this agent. Polymyxin-B did not, however, block the cardioprotective effects of preconditioning in this canine model.

11:15

706-4 Preconditioning Shortens Action Potential Duration and Lowers Ventricular Fibrillation Threshold in Pig Hearts

Michel Ovize, Jean F. Aupetit, Gilles Rioufol, Joseph Loufoua, Xavier André-Fouët, Yves Minaire. *Hopital Cardiologique, Lyon, France; University Claude Bernard, Lyon, France*

Preconditioning (PC) prevents ventricular fibrillation (VF) in the rat heart. We sought to determine whether this protective effect might: (1) apply to the pig heart, (2) be related to modifications of electrophysiologic parameters. Forty-eight anesthetized pigs underwent 40 min of LAD coronary artery occlusion (CO) followed by 2 hours of reperfusion (R). Prior to this, PC hearts received 10 min of CO and 10 min of R. Area at risk and infarct size were measured by injection of blue dye and triphenyltetrazolium staining, respectively. Duration of subepicardial monophasic action potential (MAPD) and VF threshold were measured at different time points of the experiment. As expected, infarct size was significantly reduced in PC hearts, averaging 6 ± 4%* of the risk region versus 28 ± 4% in controls (* $p < 0.01$). But, incidence of VF was not reduced in the PC group: 69% vs 63% in the control group (p = NS). Furthermore, time to VF during the 40 minute CO was significantly shorter in PC than in control hearts: 7 ± 2 min* vs 18 ± 2 min (* $p < 0.01$). This was associated with a significantly lower VF threshold and shortening of MAPD in PC hearts at the onset of the sustained CO. At 3 min of ischemia, VF threshold averaged 2.3 ± 1.7 mA(* in PC vs 4.1 ± 2.4 mA in controls (* $p < 0.01$ vs control). MAPD averaged 197 ± 4 ms* in PC hearts versus 214 ± 4 ms in controls (* $p < 0.05$). This suggests that preconditioning does not prevent but accelerates ventricular fibrillation in pig hearts via a decrease of the fibrillation threshold and a shortening of monophasic action potential during the first minutes of the sustained ischemia.

11:30

706-5 Calcitonin Gene-related Peptide Improves Recovery from Reversible Myocardial Ischemia

Ravi N. Samy, Scott C. Silvestry, B. Zane Atkins, James W. Davis, R. Eric Lilly, David C. Sabiston, Jr., Donald D. Glower. *Duke University, Durham, NC*

Calcitonin gene-related peptide (CGRP) has been found to have inotropic properties and a short half-life. CGRP has been demonstrated to reduce ischemic injury in tissue flaps as well as to increase coronary artery flow, while other available inotropes have been shown to impair recovery from myocardial ischemia. Yet, a therapeutic role for CGRP in myocardial ischemia has not been defined. Therefore, CGRP was compared to placebo in nine chronically instrumented conscious dogs who underwent two 15 minute left anterior descending coronary artery occlusions separated by at least 24 hours of reperfusion. Left ventricular transmural pressure and myocardial segment length were measured at control and during reperfusion. Either CGRP (0.07 μg/kg/min) or saline placebo was randomly chosen and continuously infused from 45 to 105 minutes of reperfusion. The alternative infusion was given during the second study. Regional function was assessed using preload recruitable work area (PRWA), a load-insensitive measure of regional myocardial performance. PRWA was calculated as the area beneath the linear stroke work vs. end-diastolic length relationship. Data are mean PRWA (% of con-

trol) ± SEM for the 9 dogs.

	90 Min	3 Hours	8 Hours	24 Hours
Placebo	89 ± 7	82 ± 8	94 ± 10	79 ± 7
CGRP	*155 ± 22	*115 ± 9	*118 ± 12	*108 ± 15

* $p < 0.05$ vs. placebo

Despite a short half-life of less than 30 minutes, CGRP caused a significantly more rapid return of cardiac function from ischemia than placebo throughout the entire 24 hours of reperfusion. These results suggest that CGRP may improve recovery from reversible myocardial ischemia and may have unique properties as an intravenous inotrope in an intensive care unit setting because it does not appear to impair recovery from acute myocardial ischemia.

11:45

706-6 Endothelin-1 Receptor Antagonists BQ123 and BQ610 Delay Ischemic Contracture, Preserve High-Energy Phosphate Metabolism and Improve Systolic Function During Ischemia/Reperfusion

Hong Han, Barbara Braeker, Stefan Neubauer, Georg Ertl. *Department of Medicine, Würzburg University, FRG*

Using specific Endothelin-1 (ET-1) antagonists BQ123 and BQ610, we tested whether endogenous ET-1 contributes to ischemia/reperfusion injury in isolated, Langendorff-perfused rat hearts. BQ123 (7 μg/min) and BQ610 (1.75 μg/min) did not affect mechanical function or coronary flow and shifted the dose-response curve for ET-1 significantly to the right. Isovolumic rat hearts were pre-treated with BQ123, BQ610 or saline for 10 min, and were subjected to 30 min ischemia followed by reperfusion. At 15 min ischemia, the increase of left ventricular resting pressure (mmHg) was significantly reduced by BQ 123 (17 ± 3*; n = 11) and BQ610 (17 ± 3*; n = 12) compared to saline (45 ± 7; n = 12). During reperfusion, recovery of left ventricular developed pressure (mmHg) was improved with BQ123 (23 ± 7*) and BQ610 (20 ± 3*) compared to saline (10 ± 3). In hearts pre-treated with BQ610, high-energy phosphate metabolism was continuously recorded with 31P-NMR spectroscopy (7T Bruker NMR System). ATP content (% of control) at 30 min ischemia was higher with BQ610 (20 ± 3*; n = 11) compared to saline (5 ± 2; n = 8), and creatine phosphate recovery (% of control) was improved with BQ610 during reperfusion (76 ± 7* vs 54 ± 6 with saline). Thus, endogenous ET-1 contributes to ischemia/reperfusion injury. Specific ET-1 antagonists attenuate functional and metabolic consequences of ischemia/reperfusion injury without affecting pre-ischemic workload.

*$p < 0.05$ vs. saline.

707 Heart Failure: Clinical Trials

Monday, March 20, 1995, 10:30 a.m.–Noon
Ernest N. Morial Convention Center, La Louisiane A

10:30

707-1 Short-term ACE-Inhibition and Onset and Progression of Congestive Heart Failure in Patients with Acute Myocardial Infarction

Claudio Borghi, Ettore Ambrosioni, Bruno Magnani, SMILE Investigators. *University of Bologna, Bologna, Italy*

Anterior acute myocardial infarction (AMI) is often complicated by clinical signs of CHF. We report the data of 1146 patients with anterior A.M.I. without previous history or clinical signs of CHF on admission and enrolled under the *SMILE* study. Patients were randomly allocated to a 6-week double-blind treatment with placebo (P) or zofenopril (Z) and then followed-up for 1 year. Baseline demographic characteristics were similar in Z and P group who were comparable for blood pressure, ECG pattern, peak CPK, and concomitant drug treatment. After 6 weeks the cumulative occurrence of CHF was not different in Z and P groups (13.3% vs 13.9%; p = 0.234). Clinical signs of mild to moderate CHF were present in 11.7% of the Z population and 10.2% of the P group (P = 0.178) whereas severe refractory CHF occurred significantly less in Z (1.6%) compared to P (3.6%) patients (RR = 2.3: C.I. 95% 1–3.3: p = 0.0328). After 1 year the overall occurrence of CHF was 14.8% in P and 15.4% in Z treated patients. NYHA class I was more common among Z treated patients (8.2% vs 1.5%; p = 0.021) whereas the percentage of patients in NYHA class IV was higher in P treated patients (24.3% vs 11.0%; p = 0.001). In conclusion the early and long-term development and progression of CHF can be prevented by short-term administration of zofenopril in patients with acute myocardial infarction.

10:45

707-2 Effects of Carvedilol on Left Ventricular Function and Exercise Performance in Patients with Heart Failure of Ischemic Etiology

Stephen MacMahon, Robert Doughty, Norman Sharpe, ANZ Heart Failure Research Collaborative Group. *University of Auckland, Auckland, New Zealand*

Results from several small trials in patients with heart failure of predominantly idiopathic etiology suggest that beta-blocker therapy may improve ventricular function, but the effects on exercise performance remain less certain. To determine the effects of such treatment in patients with heart failure of ischemic etiology, patients with this condition and ejection fraction (EF) <45% were randomized to treatment with carvedilol (12.5–50 mg/day) or placebo. Prior to randomization, 444 patients entered a 2–3 week run-in phase on open label, low-dose carvedilol (6.25–12.5 mg/day). 415 patients (93%) were randomized. Primary outcome variables were radionuclide measurements of EF and measurements of treadmill exercise duration (TED) using a modified Naughton protocol. Secondary outcomes included left ventricular chamber dimensions measured by M-mode echocardiography, submaximal exercise performance assessed from 6 minute walk distance (6 MWD) and NYHA functional class. After 6 months, resting heart rate was reduced by 7.1 bpm, and blood pressure was reduced by 5.1/4.5 mmHg in the carvedilol group compared to the placebo group. Results for the main outcomes are shown below as differences between carvedilol and placebo groups after 6 months of follow-up.

LV Function and Size		Exercise and Symptoms	
EF	+5.0%*	TED	−23.6 s
LVEDD	−1.5 mm†	6 MWD	−7.7 m
LVESD	−2.6 mm*	NYHA	+0.1

*$p < 0.01$; †$p = 0.04$; all others NS. EF = ejection fraction, LV = left ventricular, EDD = end-diastolic dimension, ESD = end-systolic dimension

In conclusion, 6 months of treatment with carvedilol in patients with ischemic heart failure resulted in improved ejection fraction and reduced LV chamber dimensions. However, there were no detectable changes in maximal or submaximal exercise performance or in NYHA class.

11:00

707-3 CIBIS Left Ventricular Function Sub-study: Analysis of Predictive Factors of Initial Improvement and Prognostic Value

Philippe Lechat, Hervé Lardoux, Jean-Pierre Boissel, Serge Witchitz, Martin Hetzel, Luigi Ciampricotti, Eric Chanton, Christian Mésenge, Patrice Jaillon, CIBIS Investigators. *CIBIS Coordinating Center, Pitié-Salpétrière Hospital, Paris, France*

During the Cardiac Insufficiency Bisoprolol Study (CIBIS) which evaluated beta-blockade (BB) effects on mortality in 641 patients (pts) with heart failure (mean follow up: 1.9 ± 0.8 years, SD), we studied the determinants of BB induced improvement of left ventricular function (LVF), the mechanism of which remains unclear. Echocardiographic assessment of LVF was performed at baseline (BL) in all patients and in a subgroup of 164 patients (83 on B, 81 on P) still alive 5 months after inclusion. All patients received a background diuretic and vasodilator therapy and were blindly randomized either to placebo (P) or to bisoprolol (B). Among these 164 pts, a similar proportion in both groups presented with left bundle branch block (23 on P, 22 on B, NS) or chronic atrial fibrillation (15 on P, 10 on B, NS). According to all recorded parameters at baseline, this subgroup of pts was representative of the entire CIBIS population. Results (means ± SD):

		EDD (cm)	ESD (cm)	FS (%)
BL	P	6.8 ± 0.9	5.7 ± 0.9	16.8 ± 4.6
	B	6.9 ± 0.8	5.8 ± 0.8	15.5 ± 5.0
5 M	P	6.8 ± 1.0	5.7 ± 1.0	16.8 ± 5.8
	B	6.7 ± 0.9	5.4 ± 1*	20.1 ± 7.0**

EDD = end diastolic diameter; ESD = end systolic diameter; FS = fractional shortening; * p = 0.07; ** p = 0.001

LVFS significantly improved on B at 5 months compared to P (LVFS variation was: −0.04 ± 5.5% with P and +4.6 ± 6.5% with B, $p < 0.001$). Such improvement was similar in ischemic and non ischemic pts. It was uncorrelated to other BL parameters and to B induced bradycardia (−18 ± 12 beats/min at 5 M), but it was significantly correlated with survival after the initial 5 month period (Cox model, 12 patients died on P, 7 on B, p = 0.01).

We conclude that echocardiographic LVFS improvement on B is an independent marker of BB action in heart failure appears uncorrelated to baseline parameters but is associated with a better prognosis.

MONDAY AM